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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,329	02/15/2006	Gunter Stempfer	BPG33319ASZB	2915

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,329	STEMPFER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 6/9/08 was entered.

Amended claims 1 and 3-22 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 102(e) as being anticipated by Kwon et al (US 2004/0151695 A1; IDS) was withdrawn in light of Applicant's amendment.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1 and 3-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Amended independent claim 1 recites the limitation "**and maintaining the medium under defined conditions of temperature and pH prior to extraction of the polypeptide**". As written, the amended claim 1 and its dependent claims **encompass**

an embodiment of a method for the preparation of a recombinant polypeptide in which the fermentation medium, not necessarily with the prokaryotic cell, is maintained under defined conditions of temperature and pH prior to extraction of the polypeptide; including a sub-embodiment in which the fermentation medium is concentrated by centrifugation or microfiltration (normally cells are separated from culture medium supernatant) prior step b), and wherein step b) the medium is maintained under defined conditions of emperature and pH prior to extraction of a recombinant polypeptide (claim 15). In the amendment filed on 10/24/07, Applicants did not cite any specific written support for this particular embodiment in the instant broadly amended claims. On the contrary, throughout the specification as filed the harvest fermentation broth including both a prokaryotic host cell and a fermentation medium; **and not the fermentation medium alone**, is maintained under defined conditions of temperature and pH prior to extraction of the polypeptide secreted in the periplasm of the prokaryotic host cell (see at least page 7, first full paragraph; page 9, last paragraph; page 10, first two paragraphs; and examples 1-3). Additionally, the specification teaches explicitly that subsequent to centrifugation or microfiltration, **the concentrated cell paste, and not the fermentation medium**, is maintained under defined conditions of temperature and pH prior to extraction of a recombinant polypeptide (see at least examples 1-3). Thus, there is **no written support** in the originally filed specification for the method as encompassed broadly by the presently amended claims.

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate and/or had possession of the instant broadly claimed invention at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claims 3-8 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Amended claims 3-5 and 13 recite the limitation "the further processing of the fermentation medium" in lines 1-2 of the claims. There is insufficient antecedent basis for this limitation in the claim. This is because in independent claim 1 from which these claims are dependent on, the only recited further processing is the further processing of the host cell in the fermentation medium; and not of the further processing of the fermentation medium.

Amended claims 6-8 recite the limitation "the interruption of the further processing of the fermentation medium" in lines 1-2 of the claims. There is insufficient antecedent basis for this limitation in the claim. This is because in independent claim 1 from which these claims are dependent on, the only recited interruption is the interruption of the further processing of the host cell in the fermentation medium; and not of the interruption of the further processing of the fermentation medium.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1, 3-14 and 16-22 are still rejected under 35 U.S.C. 102(b) as being anticipated by Bochner et al (US 4,680,262; IDS) for the same reasons already set forth in the Office Action mailed on 4/24/07 (pages 3-4). ***The same rejection is restated below.***

Bochner et al discloses a method for the preparation of hGH from transformed *E. coli*, said method comprises culturing a transformant of *E. coli* W3110 tonA, phoA, phoT containing pAP-STII-hGH in 500 mL LB medium and O tetracycline at 37 ^{0}C for 8 hrs (please note that during this time period hGH is secreted into the periplasm of the transformed *E. coli* host cells and that the transformed cells are concentrated due to growth); followed by seeding the 500 mL inoculum culture into the 10L fermenter containing phosphate-limiting medium at 37 ^{0}C (about 25 ^{o}C) and pH 7.5 for 36 hours (about 24 hour or about 48 hours); after which 1-butanol is added to the fermenter and steam is immediately injected into the fermenter jacket so that the temperature of the tank rises rapidly to 50 ^{0}C, and it is held at this temperature for 10 minutes (see example 8). Then, the fermenter is rapidly cooled below 20 ^{0}C and the cellular contents of the fermenter are harvested by centrifugation. The cell paste, is first frozen at –20 ^{0}C

and then transferred to –80 ^{0}C until further processing is required (col. 5, lines 4-51). Please note any of the steps following fermenting the transformant bacteria in 500 mL culture medium is considered to be an interrupting step prior to extraction.

Accordingly, the teachings of Bochner et al meet every limitation of the instant broadly claims. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 10/24/07 (pages 6-7) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that "interruption" is clearly and expressly stated to be a period of time occurring after completion of fermentation, and before further processing of the fermentation harvest broth. Applicants further cited 7th paragraph on page 4 to show that the interruption period of the presently claimed methods occurs after the phase of cell growth and expression/secretion of the heterologous polypeptide, and before the steps of extraction and isolation of the heterologous polypeptide. Accordingly, the Bochner et al reference does not teach a method comprising an interruption between fermentation and further processing of the harvest broth of any significant length of time. Applicants also cited the paragraph in col. 4, lines 41-46 in the Bochner et al reference to argue that the "fermentation" period taught by Bochner et al is the entire period of cell growth and accumulation of the heterologous polypeptide in the periplasm, terminated by killing the cultured cells; and none of the steps described

in example 8 of the reference falls within the meaning of the term "interrupting further processing" as used in the present claims.

Firstly, please note how the as-filed specification defines broadly the term "interrupting of the further processing". On page 7, first full paragraph states "**Said interruption of the further processing may be accomplished, for example, by maintaining, retaining, keeping or storing the fermentation harvest broth for at least one hour under appropriate conditions which ensure as far as possible the integrity of the produced polypeptide, i.e. that is not degraded or otherwise impaired in function or structure. This can be achieved, for instance, by maintaining, retaining, keeping or storing the fermentation harvest broth either in the fermentation tank (fermenter) or transferring said fermentation harvest broth into another tank or any other suitable container after collection from the fermenter. Furthermore, the fermentation harvest broth may be stirred periodically or continuously during the interruption step**". It should be further noted that there **is no requirement whatsoever that the secretion of a recombinant polypeptide into the periplasm of a prokaryotic host cell in the fermentation harvest broth is terminated or stopped during the "interrupting of the further processing" stage of the claimed method as broadly defined by the present application**. Accordingly, any of the steps following fermenting the transformant bacteria in 500 mL culture medium disclosed in the Bochner et al reference is considered to fall within the scope of the step "interrupting the further processing of the host cell in the fermentation medium".

Secondly, **the claims do not require in any shape and/or form that fermentation must be completed in step a) prior to step b), and/or in step b) the secretion of a recombinant polypeptide in the periplasm of a prokaryotic host cell should not occur to any degree**.

Thirdly, with respect to any significant length of time unless the claims recite a specific period of time, the teachings of Bochner et al meet the limitation of the broad claims. Additionally, any step that is taught in the method of Bochner et al is clearly a designed part of the method.

Fourthly, it should also be noted that the paragraph in col. 4, lines 41-46 in the Bochner et al reference cited by Applicants **is a preferred embodiment**; and that the teachings of Bochner et al are not necessarily limited to a preferred embodiment.

Accordingly, amended claims 1, 3-14 and 16-22 are still rejected under 35 U.S.C. 102(b) as being anticipated by Bochner et al (US 4,680,262; IDS) for the reasons set forth above.

Amended claims 1, 6-8, 14 and 16-21 are still rejected under 35 U.S.C. 102(b) as being anticipated by Hauptmann et al (US 5,710,027; IDS) for the same reasons already set forth in the Office Action mailed on 4/24/07 (pages 4-5). ***The same rejection is restated below.***

Hauptmann et al discloses a process for preparing IFNalpha, particular human IFNalpha2c, by recombinant expression and secretion of the protein into the periplasmic space in *E. coli* (see at least the Summary of the Invention). Hauptmann et al further

teaches a process by exemplification in which prior to the extraction step, the fermentation mixture was cooled down to about 10 ^{0}C and at the same time the pH was adjusted to 2.0 using H_2SO_4, and the biomass was separated off by centrifuging and stored frozen at –70 ^{0}C (see example 2, particularly col. 13, lines 61-67). Please also note that prior to the cooling step, the fermentation harvest broth is concentrated due to the growth of the transformed bacteria.

The teachings of Hauptmann et al meet every limitation of the instant claims. Accordingly, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 10/24/07 (page 8) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the Hauptmann et al reference does not teach an interrupting period within the meaning the term "interrupting further processing" as used in the present claims, after the fermentation step, and prior to the extraction step. Applicants further argue that the example 2 cited by the examiner only covers the fermentation stage of the process, which was ended by inactivating the biomass mixture by cooling and adjusting the pH, and separating the biomass from the fermentation by centrifugation.

Once again, please note how the as-filed specification defines broadly the term "interrupting of the further processing". On page 7, first full paragraph states "**Said**

interruption of the further processing may be accomplished, for example, by maintaining, retaining, keeping or storing the fermentation harvest broth for at least one hour under appropriate conditions which ensure as far as possible the integrity of the produced polypeptide, i.e. that is not degraded or otherwise impaired in function or structure. This can be achieved, for instance, by maintaining, retaining, keeping or storing the fermentation harvest broth either in the fermentation tank (fermenter) or transferring said fermentation harvest broth into another tank or any other suitable container after collection from the fermenter. Furthermore, the fermentation harvest broth may be stirred periodically or continuously during the interruption step". In light of a broad definition of the term ""interrupting of the further processing", the steps of cooling down the fermentation mixture to about 10 ^{0}C and at the same time the pH was adjusted to 2.0 using H_2SO_4, and the biomass was separated off by centrifuging and stored frozen at –70 ^{0}C, all of which are prior to the extraction step and fall within the scope of the instant broad claims as written.

Accordingly, amended claims 1, 6-8, 14 and 16-21 are still rejected under 35 U.S.C. 102(b) as being anticipated by Hauptmann et al (US 5,710,027; IDS) for the same reasons set forth above.

Amended claims 1, 3, 6-9, 14 and 16-22 are still rejected under 35 U.S.C. 102(b) as being anticipated by Hart et al (Bio/Technology 12:1113-1117, 1994; IDS) for the

same reasons already set forth in the Office Action mailed on 4/24/07 (page 5). ***The same rejection is restated below.***

Hart et al discloses a new method for *in situ* isolation of periplasmic human IGF-I from recombinant *E.Coli*, said method comprises the *in situ* solubilization procedure entailing the steps of adjusting the pH of the fermentation broth to pH10 and the addition of urea and DTT to a respective final concentration of 2M and 10 MM; followed by an incubation at 37 ^{0}C for about 1 hour, then cooled to 22 ^{0}C, about 20 ^{0}C (see at least the abstract and particularly page 1116, right column, first two full paragraphs). The *in situ* solubilization procedure is an interrupting procedure prior to the aqueous two-phase extraction.

The teachings of Hart et al meet all the limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 10/24/07 (page 9) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the 1-hour solubilization procedure taught by Hart et al does not fall within the meaning of "interrupting further processing" of the instant claims.

Once again, please refer to the broad definition of the term "interrupting of the further processing" by the instant specification as discussed above. In light of a broad

definition of the term ""interrupting of the further processing", the *in situ* solubilization step prior to the extraction step that is taught by Hart et al. falls within the scope of the instant broad claims as written.

Accordingly, amended claims 1, 3, 6-9, 14 and 16-22 are still rejected under 35 U.S.C. 102(b) as being anticipated by Hart et al (Bio/Technology 12:1113-1117, 1994; IDS) for the reasons discussed above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633